First appearance of "Hexamethonium man" ← p. (56)

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VIII

The Principles of Ganglionic Block

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In this lecture I would like to reverse the usual logical order of such a talk and to start by describing briefly some of the practical applications of ganglion blocking agents before discussing the pharmacological principles involved in their use. For the position is now somewhat as follows: it was first shown in the laboratory that such drugs were suitable for clinical trial; then these clinical trials proved sufficiently promising to make it worth carrying on with therapeutic investigations, and at the same time raised a number of new problems. As a result, whereas two or three years ago the laboratory worker was asking the clinician to try this or that substance, now it is the clinician who turns to the laboratory worker for interpretation of his results.

The main uses of hexamethonium, which I shall take as the prototype of ganglion blocking agents for the moment, have been in the treatment of *hypertension*, in *gastroenterology*, and in the *reduction of bleeding* at operation. Thus, in a patient suffering from hypertension, his blood pressure may be greatly reduced, his enlarged heart get smaller, his pulmonary oedema regress, and his vision, impaired by retinal damage, improve. Similarly in peptic ulcer hexamethonium produces a reduction of acid secretion and a depression of the exaggerated motility of the gut. The third use mentioned is in some ways the most interesting. If the blood pressure is reduced during a surgical operation to levels of about 60–70 millimetres systolic, bleeding can be enormously lessened. This was done in the past either by giving the patient a deliberate haemorrhage, or by inducing spinal anaesthesia.

But both of these methods have considerable disadvantages, and it has proved possible to achieve the same end by giving a dose of hexamethonium and then tilting the patient so the blood may accumulate in the lower part of his body. When this technique is successful, very dry fields of operation can be obtained, which make plastic surgery much easier and quicker, and neurosurgery a great deal simpler; sometimes, in fact, the use of controlled hypotension may make possible operations otherwise almost too hazardous to undertake.

But each of these uses has raised problems. In *hypertension* we have the difficulties that oral dosage is relatively inefficient, that patients vary enormously in their response, and that patients on hexamethonium for a relatively prolonged period develop an increasing resistance to its hypotensive action. Similarly in the use of hexamethonium in *gastro-intestinal disease*, where it has been used to depress the motility of the small intestine, it has been found to cause distension of the gut, partly simply by delaying its emptying but partly, it appears, by doing something else, such as interfering with absorption of fluid. Finally, the use to diminish *bleeding* at operation raises the question of why it is that a patient may have his pressure lowered so far without suffering any ill-effects, and the additional practical question of how to make it possible to achieve these reductions of blood pressure more uniformly.

These are the sort of problems which arise, and others will no doubt appear in the future; and it is with such questions in mind that we must turn to consider the sort of knowledge needed to be able to handle ganglion blocking agents with some hope of success. This may be summarized briefly as knowledge about (1) the properties of the transmission process in autonomic ganglia; (2) the properties inherent in quaternary salts; (3) normal autonomic background tone and reflex activity; (4) the reactions of the body to autonomic paralysis.

1. The Mechanisms of Ganglionic Transmission and Block

The autonomic ganglia receive from the central nervous system preganglionic trunks which enter the ganglia, and there synapse with the cells from which the postganglionic trunks take origin.

The electrical activity accompanying a nerve impulse in the preganglionic trunk causes, when it reaches the terminations of the preganglionic nerve, a discharge of acetylcholine (Feldberg and Gaddum, 1934). This impinges on the ganglion cell body, which appears to be specifically differentiated so that it responds to this acetylcholine by a vigorous electrical discharge. This is sufficient, in turn, to excite a further impulse in the postganglionic nerve trunk of the same type as that which, in the preganglionic trunk, initiated the whole chain of events. In normal transmission the cycle of events is complete in a fraction of a second, and the electrical activity of the ganglion has completely subsided within 100–400 milliseconds (Eccles, 1935). This is because acetylcholine, as soon as it has achieved its excitation of the ganglion cell body, is then either destroyed by the cholinesterase located at the preganglionic nerve terminals, or diffuses away from the site of action, to be rapidly diluted in the surrounding tissue space.

Because the chain of transmission involves a chemical link at this point, it is vulnerable to a chemical attack. First we may have substances bearing a chemical relationship to acetylcholine sufficient to give them some affinity for the ganglion cell membrane, but lacking the additional ability of actually initiating excitation. Such compounds, it is believed, then simply compete with acetylcholine for the ganglion cell receptors, thus rendering acetylcholine less effective than usual. If these compounds are present in sufficient concentration they may reduce the effect of acetylcholine below that required to initiate impulses in the postganglionic trunk, so that ganglionic transmission fails. A block of this kind, which is exerted by drugs such as d-tubocurarine, T.E.A. and hexamethonium, is termed a *competitive* block, and these drugs are *competitive* blocking agents.

But another type of block is also possible. A drug may actually be able to mimic acetylcholine completely but to be unsusceptible to the action of cholinesterases. In that case it excites the ganglion for much longer than the fraction of a second involved in normal transmission and this is accompanied by a prolonged *depolarization* of the ganglion cell membrane (Paton and Perry, 1953). With this prolonged excitation of the postganglionic nerve trunk, there results finally a condition where acetylcholine still impinges on the ganglion cell membrane normally, but this is already maximally excited, cannot be further excited, and transmission fails. A block of this sort by nicotine or acetylcholine itself, which is always associated with an initial stimulant effect, may be termed depolarization block.

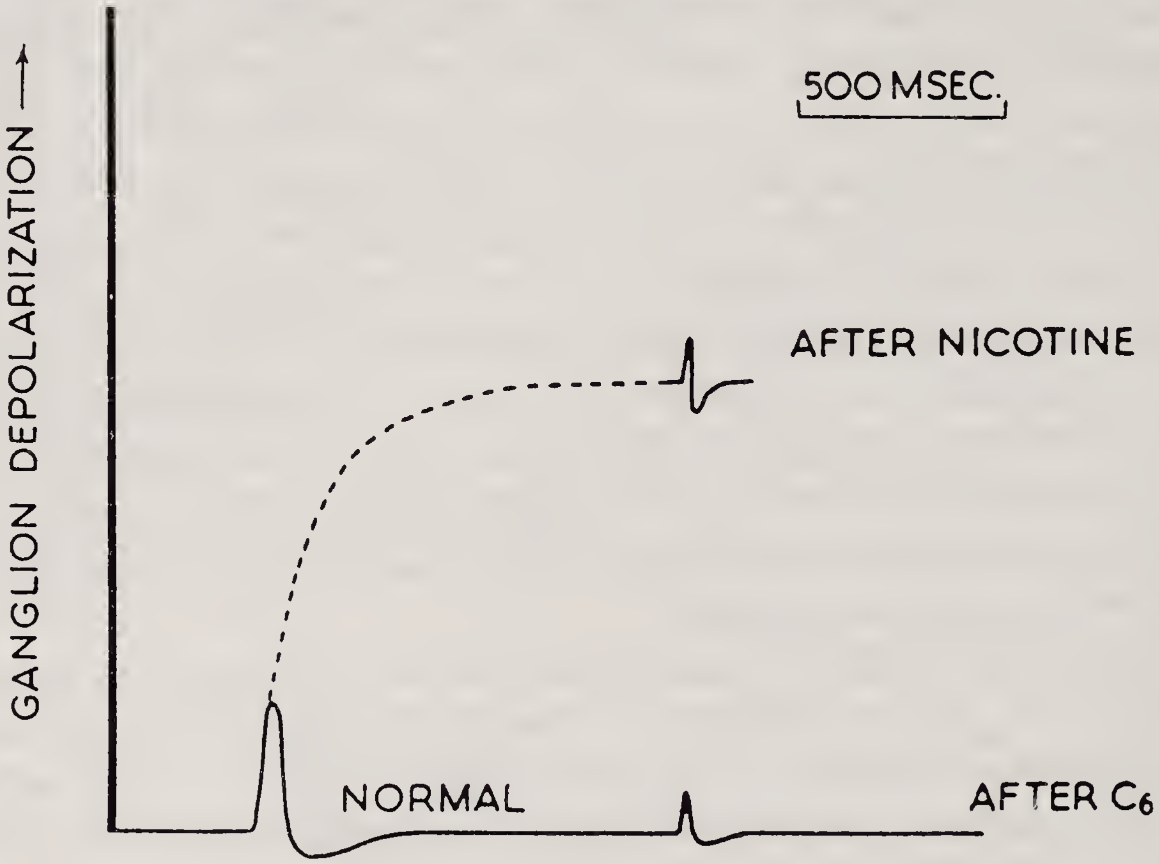


FIG. 1. Diagram of normal ganglion action potential and action potential (a) after nicotine, (b) after hexamethonium. With nicotine the ganglion is depolarized, as though a normal excitation had persisted; with hexamethonium the ganglion is not depolarized.

A third type of intervention with ganglionic transmission may arise in a different way. It is known that some substances, including the local anaesthetic procaine and its stable analogue procaine amide, can interfere with the release of acetylcholine from the preganglionic nerve terminals (Harvey, 1939; Paton and Thompson, 1953). This is not associated with any chemical resemblance of procaine to acetylcholine, and the 'pharmacological lesion' is of a different kind to the others already mentioned; it may be attributed to a particular susceptibility to local anaesthetics on the part of the delicate nerve terminals. A development of particular interest is the clinical combination of procaine amide with hexamethonium. The former has been shown in animals and in man to synergize with hexamethonium in producing ganglionic block (Mason and Pelmore, 1953). It indicates a potentially valuable way of supplementing the action of a competitive ganglion blocking drug.

TABLE 1. Types of Ganglionic Block

Characteristics	Competition with acetylcholine	Depolarization	Prevention of acetylcholine release
Release of acetylcholine	Normal	Normal	Depressed
Response to injected acetylcholine	Depressed	Depressed	Present
Initial action	Block	Stimulation	Block
Examples:	d-tubocurarine	Acetylcholine	Local anaesthetics
	T.E.A. (tetraethylammonium)	T.M.A. (tetramethylammonium)	Calcium deficiency
	Hexamethonium (C.6)		Botulinum toxin
	Nicotine (2nd phase)	Nicotine (1st phase)	

Ganglion blocking agents of the competitive type are at present the most widely used. Those acting by depolarization are not very serviceable clinically because of the initial stimulation which they produce; this means, for instance, that before being able to lower the blood pressure with a drug like nicotine, a phase of strong autonomic excitation, with a rise of blood pressure and release of adrenaline, would have to be undergone. Among the competitive blocking agents hexamethonium has so far proved most generally suitable and most of this review will refer to information gained with this substance in the clinical studies which it has made possible. But many other substances have been prepared, progeny still very like their parent in appearance, but sometimes more active and longer lasting. (No doubt hexamethonium will in due course be completely superseded; but the lessons learnt with it are likely to be of general application.) Another competitive ganglion blocking agent is tetraethylammonium, with which interest in ganglion blocking agents in recent years was first aroused (Acheson and Moe, 1945–6); it still has a place in investigation for its transience of action. But, as we shall see, its action is complicated in some degree, which detracts distinctly from its value.

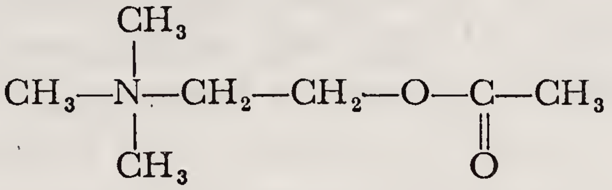
The use of hexamethonium is not in practice, however, completely straightforward. This is not because the drug itself produces irregular effects when given under standard conditions to a particular autonomic ganglion; on the contrary, perfectly consistent results can be obtained in animals with almost any of these drugs. It arises because autonomic activity in man is a rather more subtle affair than was suspected. The first two complications are that ganglia differ in their sensitivity to competitive block; and that the intensity of the block is related to the frequency of excitation of the ganglia.

(i) *Selectivity and Maximality of Block.* It has in fact been known for many years that ganglia differ in their susceptibility to paralysis, whether by nicotine, d-tubocurarine or (more recently) hexamethonium. Indeed difference in sensitivity may occur between the different ganglion cells within one particular ganglion, e.g. the superior cervical ganglion. Here cells supplying the nictitating membrane seem to be resistant compared to those supplying the dilator muscles of the pupil. In animals the ganglia supplied by the chorda tympani are particularly susceptible. But no generalization about sensitivity has yet been possible; so that in clinical practice it is necessary to determine the sensitivity of a ganglion directly, and it cannot be assumed that a given dose adequate to block one particular system would also prove sufficient to block another. Some capriciousness in the incidence of block is already clear in man. For instance, paralysis of accommodation only occurs in a proportion of subjects. Some subjects develop a paralysis of the light reflex without effect on the reaction to accommodation—a pharmacological Argyll-Robertson pupil. Similarly paralysis of the bladder, or constipation, may be absent or trivial, despite the appearance of considerable reduction in blood pressure or postural hypotension.

Related to this is the observation that it is rarely possible to produce complete ganglionic block throughout the body. In particular some of the vasomotor ganglia in animals appear to

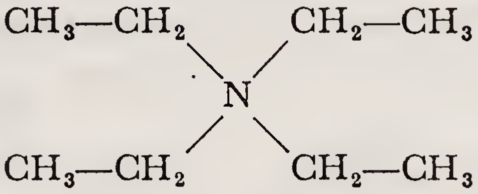
TABLE 2. The Structural Formulae of some Ganglion Blocking Agents

Acetylcholine

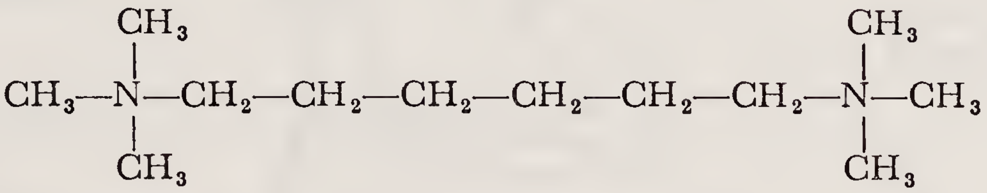


$$CH_3-\underset{CH_3}{\overset{CH_3}{N}}-CH_2-CH_2-O-\underset{\overset{\|}{O}}{C}-CH_3$$

Tetraethylammonium

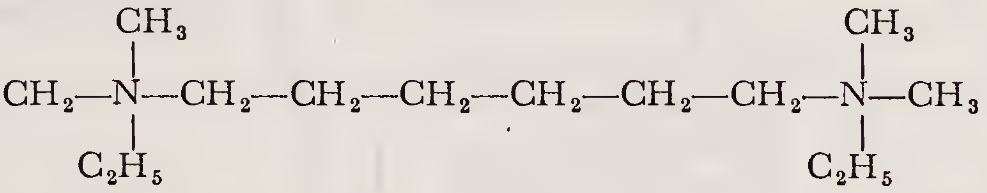


Hexamethonium



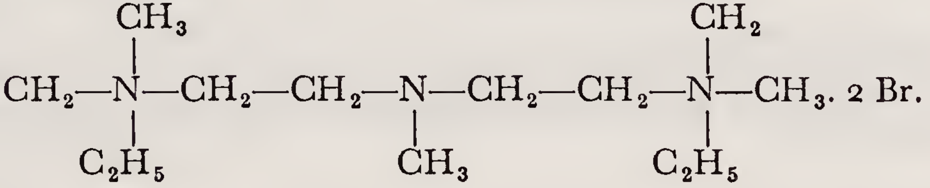
$$CH_3-\underset{CH_3}{\overset{CH_3}{N}}-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-\underset{CH_3}{\overset{CH_3}{N}}-CH_3$$

M & B 1863



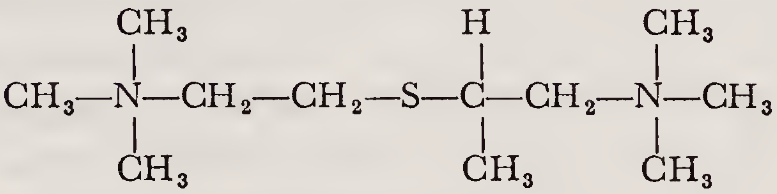
$$CH_2-\underset{C_2H_5}{\overset{CH_3}{N}}-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-\underset{C_2H_5}{\overset{CH_3}{N}}-CH_3$$

Ciba 9295 (Pendiomide)



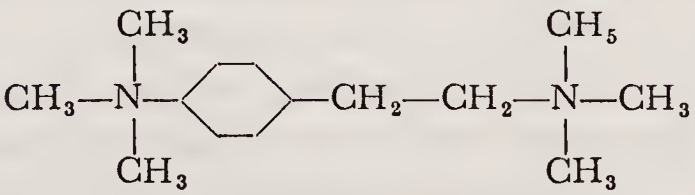
$$CH_2-\underset{C_2H_5}{\overset{CH_3}{N}}-CH_2-CH_2-\underset{CH_3}{N}-CH_2-CH_2-\underset{C_2H_5}{\overset{CH_2}{N}}-CH_3.\ 2\ Br.$$

Roche: 3–0484

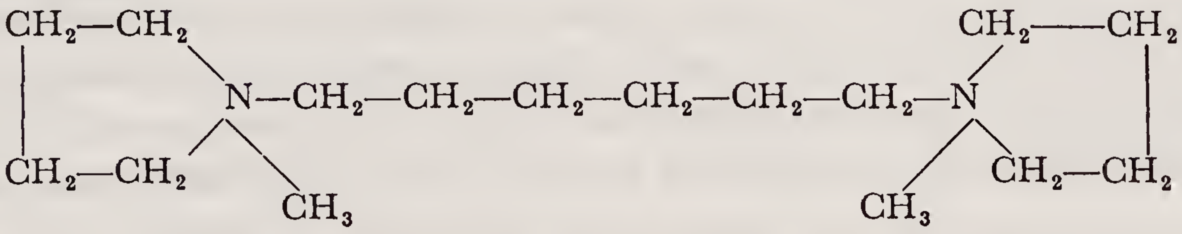


$$CH_3-\underset{CH_3}{\overset{CH_3}{N}}-CH_2-CH_2-S-\underset{CH_3}{\overset{H}{C}}-CH_2-\underset{CH_3}{\overset{CH_3}{N}}-CH_3$$

M & B 1950



M & B 2050



be very resistant to complete paralysis. This probably means that in man complete blockade will be difficult to achieve, although no doubt in particular individuals certain autonomic functions can be completely suppressed. In clinical experience it has been found that, at any rate in the lower limb, hexamethonium will produce as great an increase in blood flow as will a block of the autonomic pathways with local anesthetics. On the other hand it has proved very difficult to suppress entirely such vascular reflexes as the 'cold pressor response'.

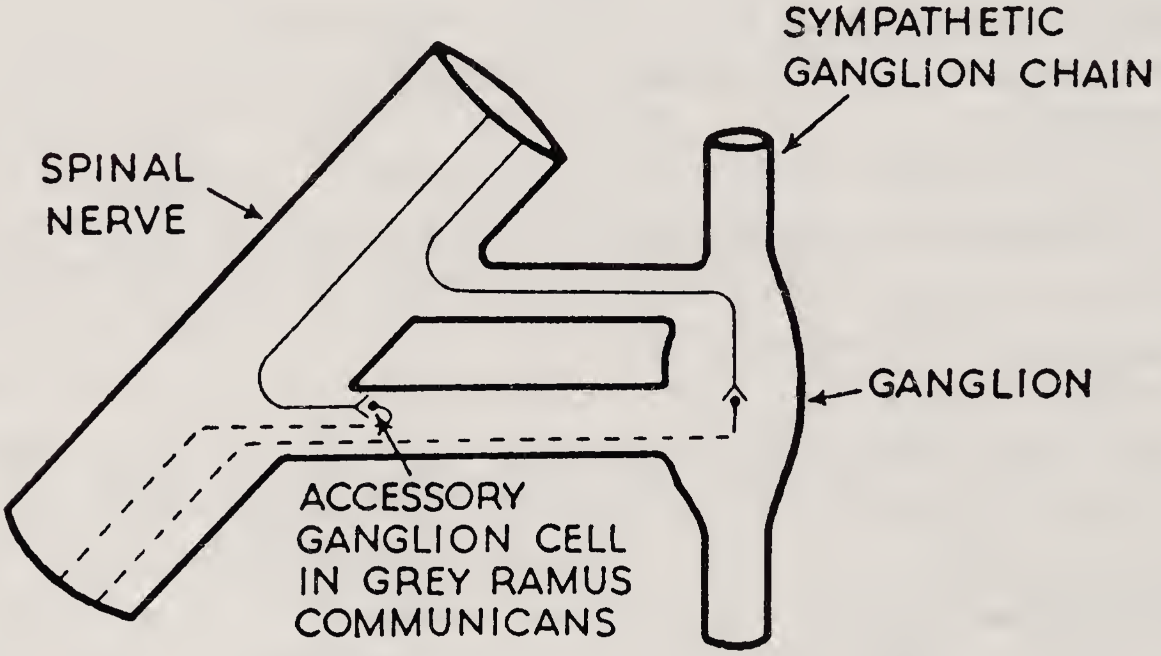
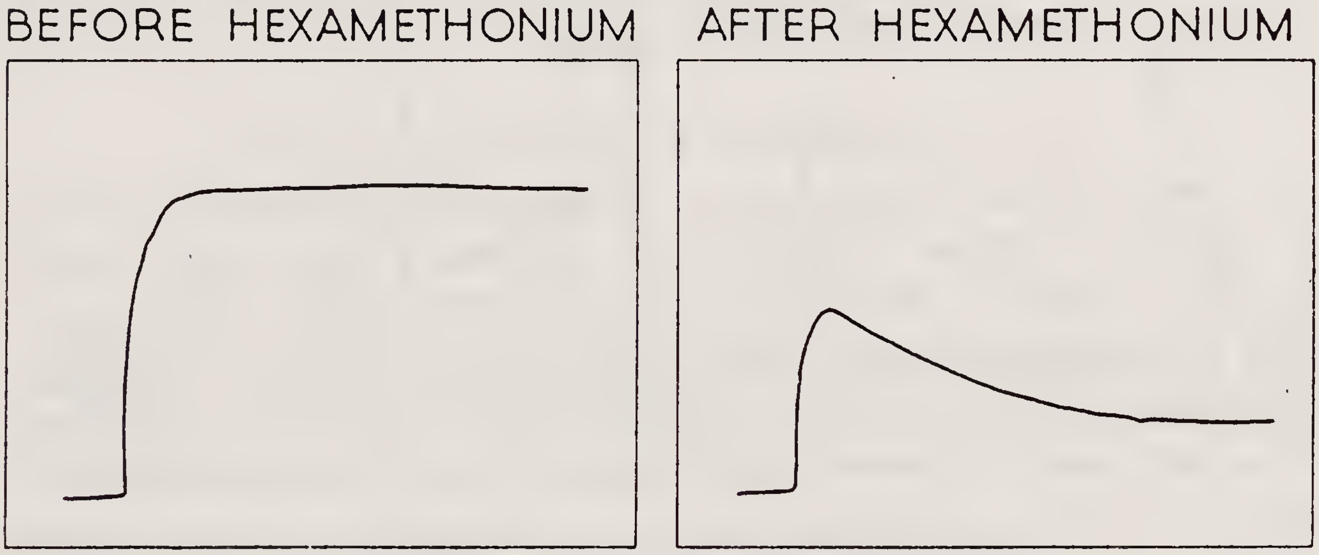

SYMPATHETIC GANGLION CHAIN
SPINAL NERVE
GANGLION
ACCESSORY GANGLION CELL IN GREY RAMUS COMMUNICANS

Fig. 2. Diagram and accessory ganglionic synapse in grey ramus communicans. Continuous lines show preganglionic trunks; dotted lines the postganglionic trunks.

There is an interesting analogy here with the failure of surgical sympathectomy to be complete. This has been shown to be due to the existence of a considerable number of sympathetic ganglion cells outside the main paravertebral trunks (Boyd and Monro, 1949); they are found, for instance, in the rami, and in the spinal nerves, positions often inaccessible to the surgeon. Fig. 2 illustrates a typical situation, where the preganglionic trunk synapses in a grey ramus, and the postganglionic trunk dodges back (as if anticipating surgical assault) into the spinal nerve. There may be more than a superficial analogy here. These accessory ganglion cells might be regarded as being still incompletely extruded from the central nervous system, and could still be partly enclosed by the blood-brain barrier which so effectively protects the central nervous system from quaternary salts. If this were the case, the surgical and pharmacological inaccessibility would spring from the same cause—that the ganglion cells concerned still bore too close a relationship (anatomically or structurally) to the central nervous mass from which they derived.

(ii) *Fatigability.* One of the notable features of paralysis by ganglion blocking agents is the increased ease of fatigue of transmission which ensues. This may be shown in various ways. First, the block may be greater as the rate of excitation of the ganglion increases. Second the effect of a given dose of hexamethonium becomes greater, the longer excitation has been established. One may see the onset of fatigue from the earliest moment of a period of excitation (Fig. 3). The response of the effector organ (in this case the nictitating membrane) starts quite vigorously but then wanes within a few moments until quite a considerable degree of block has occurred. A similar phenomenon has been observed in man. After a moderate dose of hexamethonium, and in an individual in which this produces some interference with accommodation, the subject frequently notices that during recovery from the effects of the drug he can read successfully for half a minute or a minute, and then finds his vision becoming blurred again. A brief rest from the effort of



BEFORE HEXAMETHONIUM AFTER HEXAMETHONIUM

FIG. 3. Record of contraction of the cat's nictitating membrane, excited by stimulation of the preganglionic cervical sympathetic trunk at 10 shocks per second for one minute. Before hexamethonium and after hexamethonium, showing onset of 'fatigue'.

accommodation enables him again to see, for a short time, with clarity.

This enhanced fatigability of the partially blocked ganglion may be important clinically. For it follows that the ganglion subjected to the most intense autonomic drive may be also the ganglion most readily blocked by the drug. Thus in neurogenic hypertension or in peptic ulcer, the abnormal drive on the ganglia concerned may be preferentially weakened before other, normal, functions are interfered with. This would explain how, occasionally, very small doses (1–5 mgms.) of hexamethonium may, when first administered to a hypertensive patient, produce a very considerable fall in blood pressure.

2. The Properties of Quaternary Salts

(i) *Other Pharmacological Actions.* Besides being transmitter at the ganglionic synapse acetylcholine mediates two other transmissions at least: the peripheral parasympathetic transmission and transmission across the neuromuscular junction. Further, enzymes capable of destroying it at a very high rate are widely distributed at important points throughout the body. Most substances bearing a pharmacological relationship to acetylcholine at any one of these various points also have traces of a relationship at the other sites. One may thus construct a sort of spectrum of the activity of the drug. At each site it may imitate acetylcholine or antagonize it, or antagonize the enzyme which destroys acetylcholine. Thus quite a diverse range of actions in mimicking, blocking, or preserving the natural transmitter at the various synapses have to be considered. In addition, since these compounds are nitrogenous bases they are liable to possess other actions, such as that of histamine release. A spectrum of this kind has been constructed for *d-tubocurarine* (Fig. 4*a*) to illustrate the point. It will be seen that it possesses detectable activity at all the synapses mentioned, as well as some anticholinesterase action and the power of histamine release. *Nicotine* (Fig. 4*b*) is likewise fairly complex. With *tetraethylammonium* (Fig. 4*c*) also, although it is considerably better than these in the selectivity of its action, there are several additional effects at other sites. The fourth spectrum represented is that of

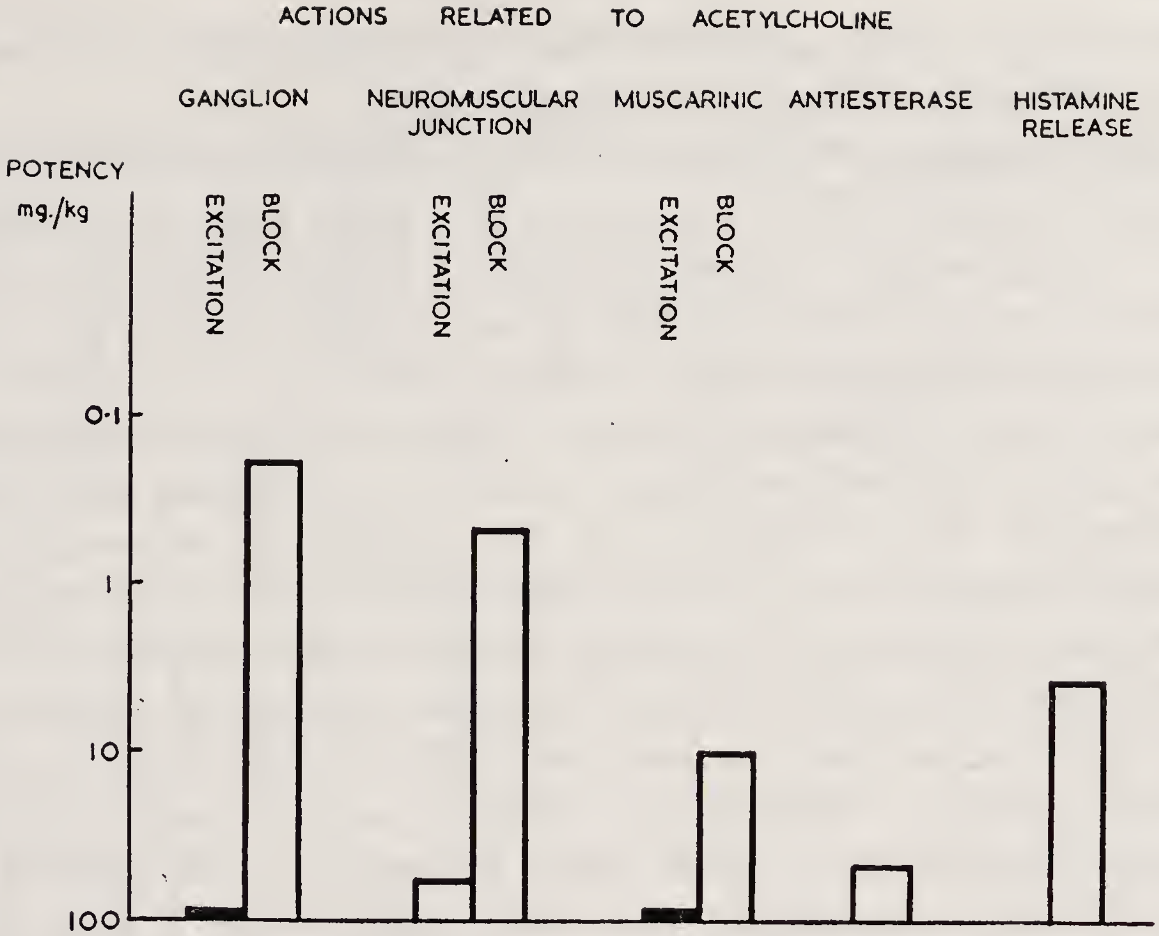


FIG. 4 (*a*). Spectrum of pharmacological actions possessed by *d-tubocurarine*. The ordinate gives the approximate potency of the drug (in mg./kg.) for each action. Only the more prominent actions are represented, and each compound (*see also b, c, d*) has a number of other properties in addition.

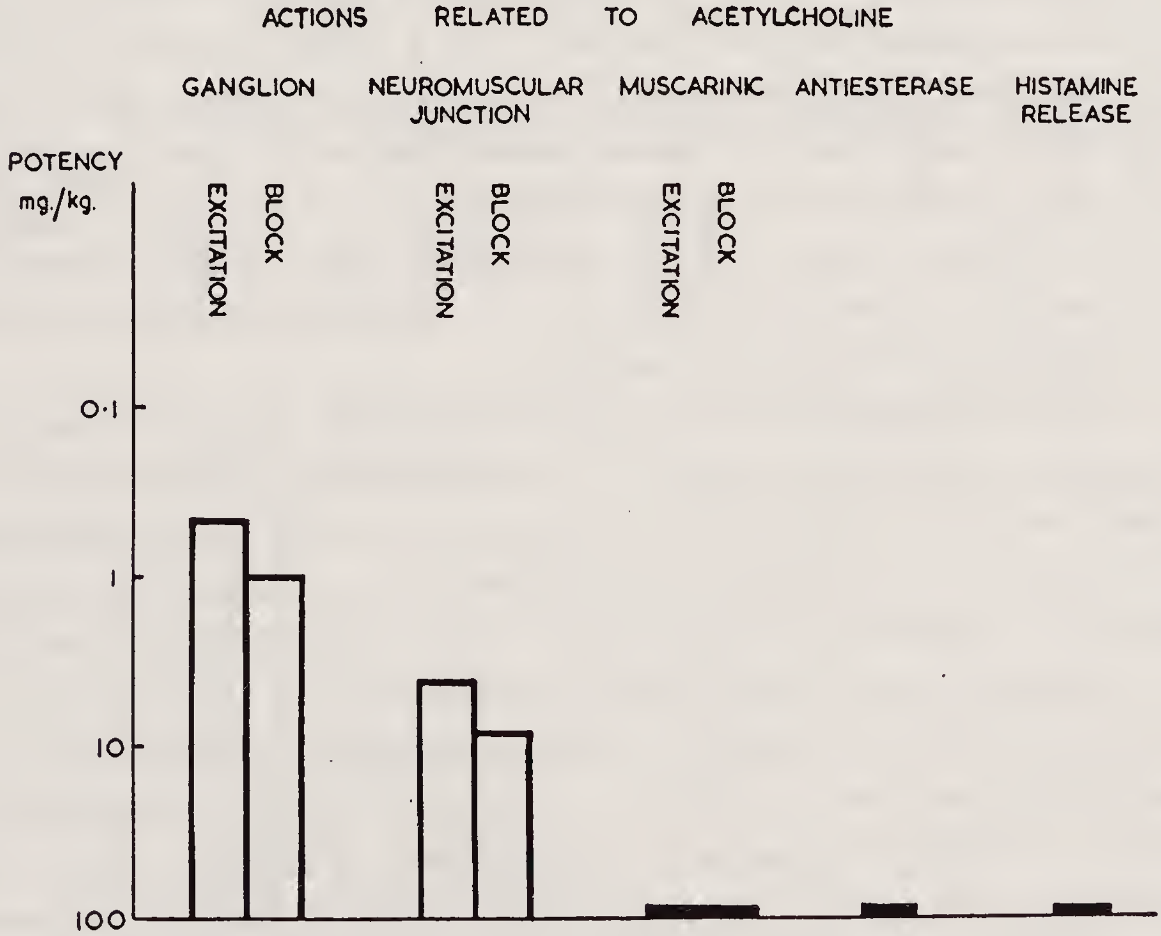


FIG. 4 (*b*). Spectrum of pharmacological actions possessed by *nicotine*.

hexamethonium (Fig. 4*d*) and illustrates its relative pharmacological cleanness (Paton and Zaimis, 1952).

The significance of a spectrum such as this lies in the use made of such drugs. It does not matter if a drug has, for instance, some atropine-like action as well as a ganglion paralysing action, if its use is to be mainly in the treatment of peptic ulcer; but investigations with such a drug will always be difficult to interpret and will throw little more light on what is happening, than can investigations using a mixture of atropine and hexamethonium. In a similar way, the ability of tetraethylammonium sometimes to elicit a secretion of adrenaline or noradrenaline, has complicated the interpretation of the results obtained with it and led possibly to some mistaken conclusions. Again, an awareness that all these actions are liable to occur in agents able to block ganglia, allows more careful scrutiny of the pharmacological background to such drugs before they are applied to man. Finally—a scientific point—the properties of a drug give information about the receptor structure at which it acts: each can be regarded as a sort of garment, whose design gives one a clue to the structure it clothes. Nicotine could be compared to one of those shapeless objects that people knit in railway trains —one has a grave doubt whether it is a baby's vest, or a seaman's stocking. But hexamethonium is more like a glove, enabling one to say that it goes on something with five fingers (or rather that it fits on to something about 7 Å wide). In our poverty-stricken state, where everyone talks about receptor structures but no one has seen one, we must be grateful even for these small clues about their nature.

(ii) *The Pharmacodynamics of Quaternary Salts.* The relationship of ganglion blocking agents to acetylcholine shows itself in another way. In order for a drug to be able to antagonize acetylcholine at the ganglionic synapse, it is necessary for it to be chemically related to acetylcholine. This implies that it must be a very strong base. This in turn entails that it shall penetrate cell membranes very slightly. This means that a drug such as hexamethonium has to lead a predominantly extra-cellular existence. It follows that it is only slowly absorbed from the intestine since there is here a complete cellular barrier between

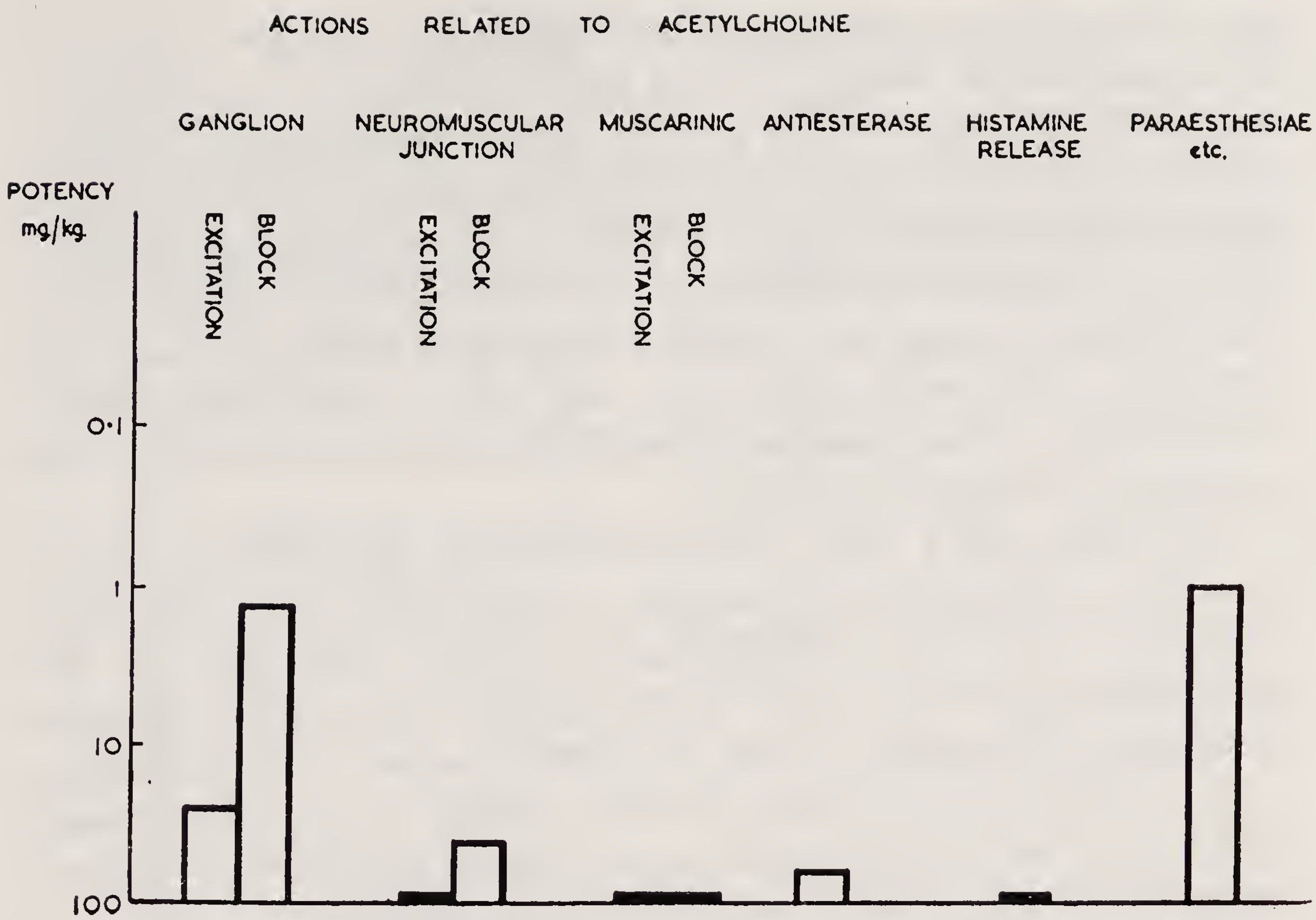


FIG. 4(*c*). Spectrum of pharmacological actions possessed by *tetraethylammonium.*

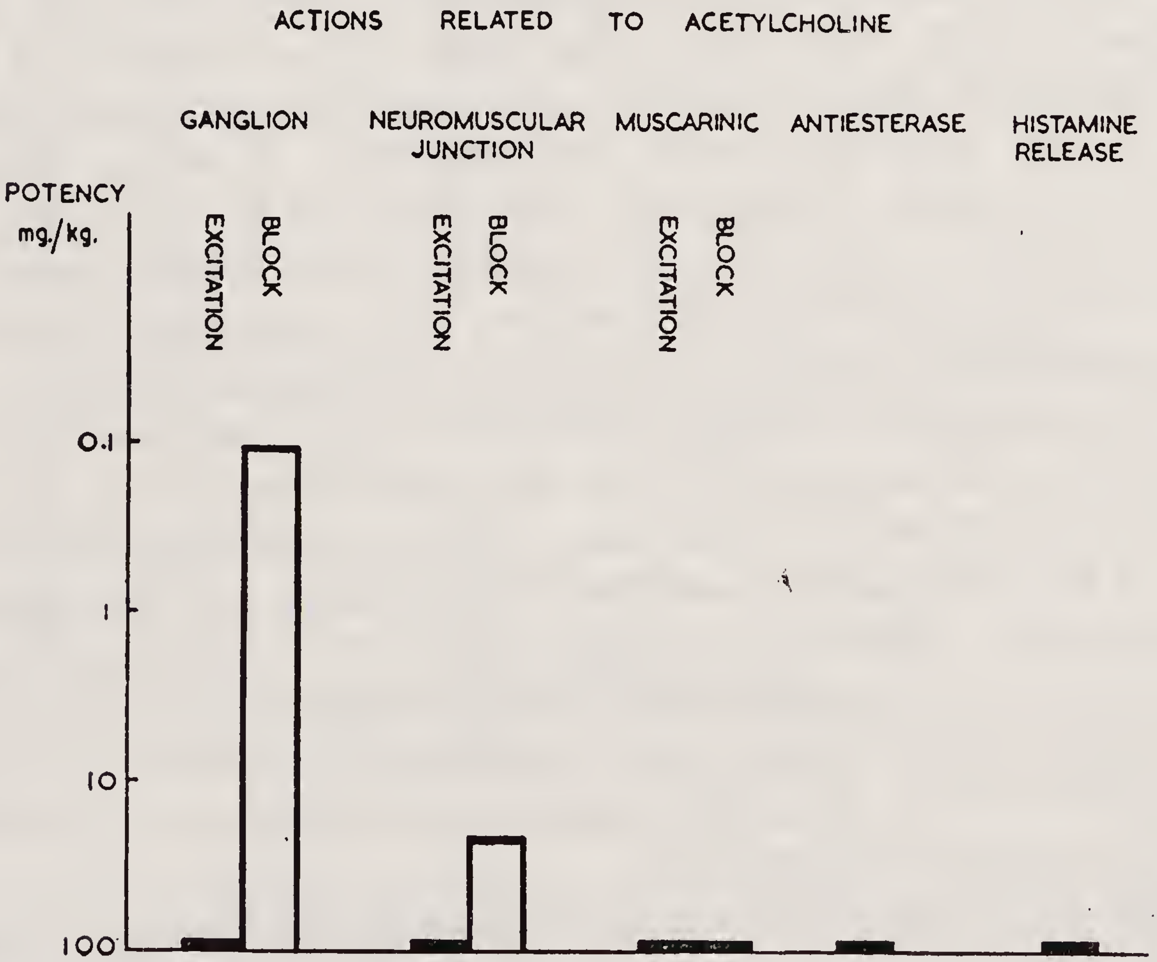


FIG. 4 (*d*). Spectrum of pharmacological actions possessed by *hexamethonium.*

the lumen of the intestine and the blood stream. When absorbed it is distributed roughly in the extra-cellular space (Morrison and Paton, 1953). While present in the blood stream it penetrates only very slightly across the cell barrier of the choroid plexus and appears only in traces in the cerebral spinal fluid (Fig. 5) (Paton, unpublished). It penetrates only slightly into the aqueous humor and into the red cells. Finally it is excreted only by glomerular filtration, and like inulin can neither traverse the renal tubules outwards by being secreted nor yet inwards by being re-absorbed.

The effects of a dose of hexamethonium therefore are determined by, amongst other factors, its absorption from the intestine, by the volume of the extra-cellular fluid and by the glomerular filtration rate of the subject concerned. Because intestinal absorption is poor and (even worse) erratic, parenteral administration is now the rule. As the drug is eliminated almost exclusively by the kidney, prolonged actions are obtained in patients with seriously impaired kidney function.

An Analysis of Variations in Sensitivity. From what has been said, it might be expected that if one took a single test (say the effect of hexamethonium on the standing systolic blood pressure), in a normal subject, then the results might vary according to the distribution of the drug in the body, but that they would relate pretty well with the plasma concentrations. A recent investigation was made of this point (Morrison and Paton, 1953), in which effects of subcutaneous injections of hexamethonium on the standing systolic blood pressure were compared with the concentration in the plasma (assayed by biological means).

It was found that subjects did indeed vary considerably both in the rate of absorption from the subcutaneous site, in the volume of distribution of the drug, and in its excretion. But these factors did not account for all the differences by any means, and considerable differences between individual responses were obtained even when the effects were plotted against the plasma concentrations. It turned out, in fact, that they differed as much as eightfold in the size of the cardiovascular response to a given plasma hexamethonium level.

Thus, even when using a single autonomic function, in normal individuals, and having eliminated all the variables of distribution and excretion, the response of the organism to a ganglion blocking drug is widely different from one individual to another. What other factors are at work? Two at least may be

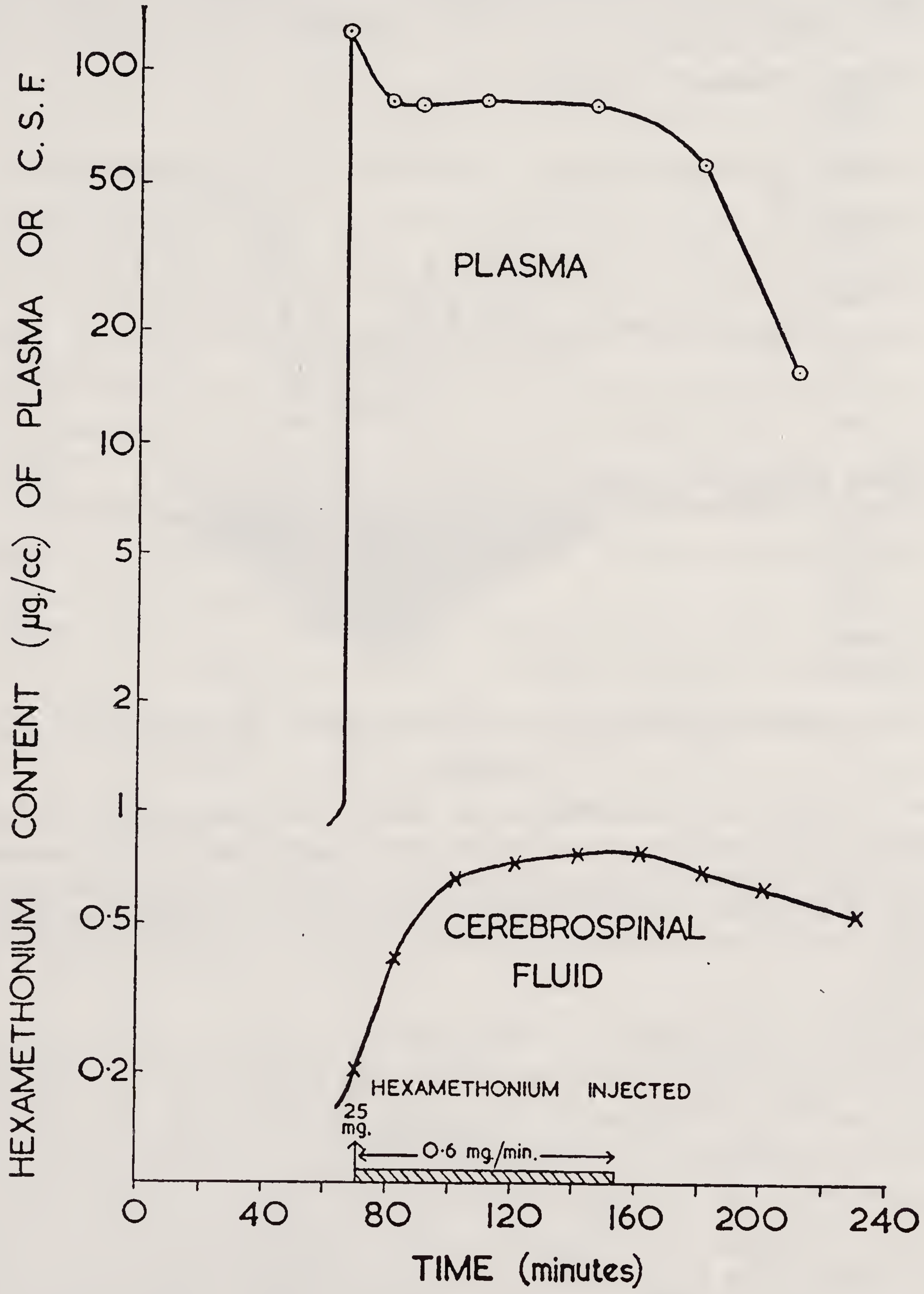


Fig. 5. Graph of the hexamethonium content of plasma (above) and cerebrospinal fluid (below) from a cat receiving repeated intravenous injections of hexamethonium. In spite of a sustained high plasma level, the cerebrospinal fluid never contains more than traces of hexamethonium.

envisaged; variations in background autonomic tone, and variations in the response to partial autonomic paralysis.

3. Autonomic Tone

The effect of a ganglion blocking agent, if this is its only significant action, is entirely indirect. When there is no natural activity traversing the autonomic pathways, then block of the ganglionic transmission in that pathway will not produce any physiological effect. For instance, in an animal whose nervous system has been completely destroyed, so that there is no longer any autonomic outflow, the administration of hexamethonium has no action at all. Our knowledge of normal tonic activity therefore becomes very important. Dr. Feldberg[1] describes in his paper the sort of pathways that exist and some of the conditions

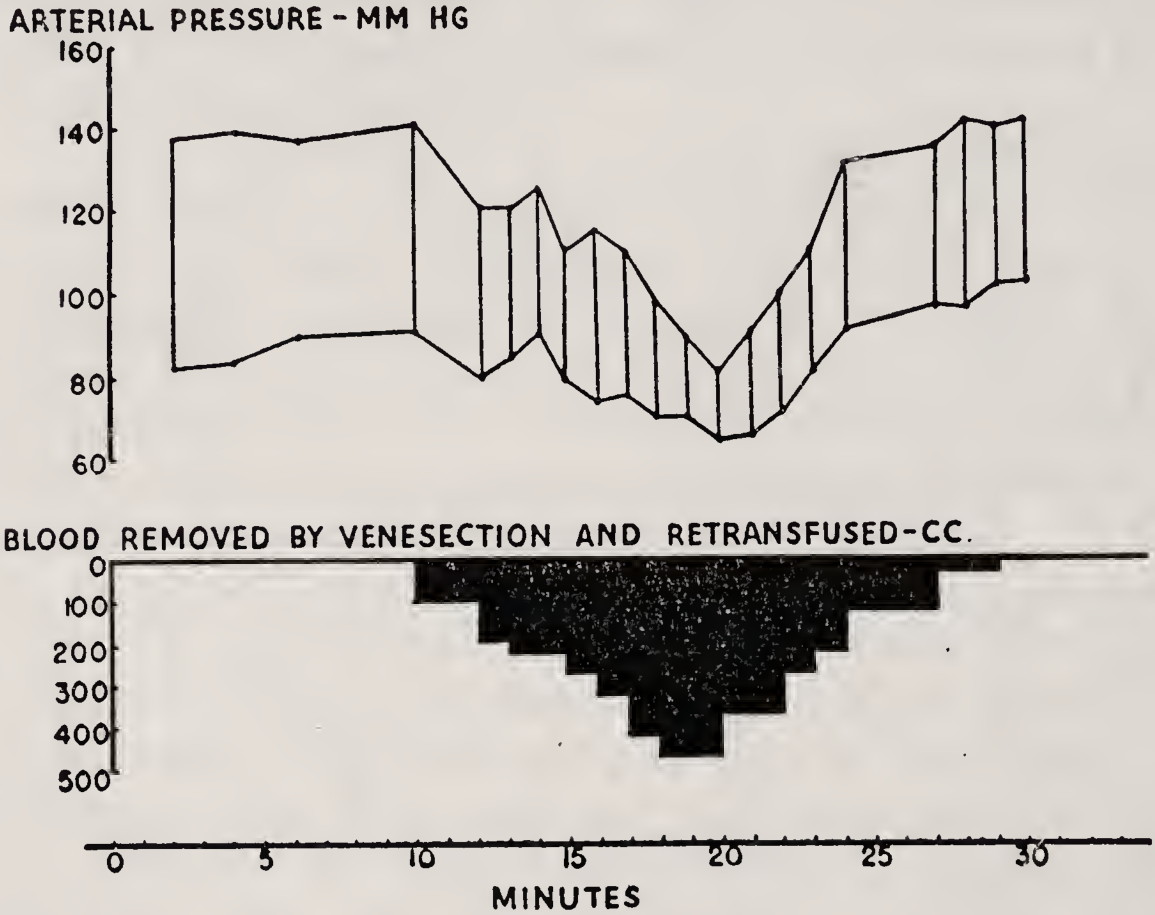


Fig. 6. Effect of withdrawing 500 cc. blood in successive steps, and then replacing it, on the blood pressure of a supine human subject after injection of 50 mgm. hexamethonium intravenously. The fall of blood pressure is roughly proportional to the amount of blood removed, and the loss of only 100 cc. is sufficient to lower the pressure significantly. (From Freis *et al.* (1951).)

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[1] *See* 'The Physiology of the Autonomic Nervous System', pages 343–47 below.

under which there is undoubtedly a vigorous activity in these pathways. Among these conditions will be many reflexes, of which a number of vascular reflexes are known to be considerably affected by hexamethonium. For instance, if one makes a violent expiration against a resistance—the so-called Valsalva manœuvre—when it is over there is quite a considerable rise in blood pressure, often called an 'over-shoot'; hexamethonium greatly reduces it. Another vascular reaction is that to haemorrhage, which is normally followed by a compensatory peripheral vasoconstriction such that a pint of blood can be withdrawn without producing more than a trivial fall of blood pressure. In the presence of hexamethonium, which prevents much of this response, the effects of haemorrhage on the blood pressure become much greater (Fig. 6) (Freis *et al.*, 1951); and the circulatory system almost behaves like a simple elastic tube in which the pressure falls as fluid is withdrawn from it and rises again when it is restored. This is an important observation because bleeding may be more dangerous in a patient treated with hexamethonium than in the normal.

A third reflex of great practical importance is the postural reflex (Fig. 7). Normally when a subject stands, the blood pressure does not fall very much and sometimes even rises slightly. To bring this about, considerable vascular re-adjustments are necessary; the blood flow diminishes to almost all organs except to the head; the cardiac output diminishes and the venous filling pressure falls. After hexamethonium this fairly wide vasoconstriction no longer takes place, or to a much reduced degree. The cardiac output is diminished on standing about as much as in the normal. Hence the arterial pressure must go down. This postural reaction to hexamethonium, due to interference by the drug with normal postural tone, is of primary importance. Its mechanism is not completely understood, and we do not know how far it arises simply because peripheral arteriolar constriction can no longer occur, or how far it is due to the accumulation of blood in the legs or abdomen, or elsewhere. We know that the blood pressure can be raised again by exercise, by standing-running, or by abdominal compression. The reaction is exploited deliberately in the treatment of hypertension and in controlled hypotension in anaesthesia; but it represents a complication in other therapeutic uses such as the treatment of peptic ulcer.

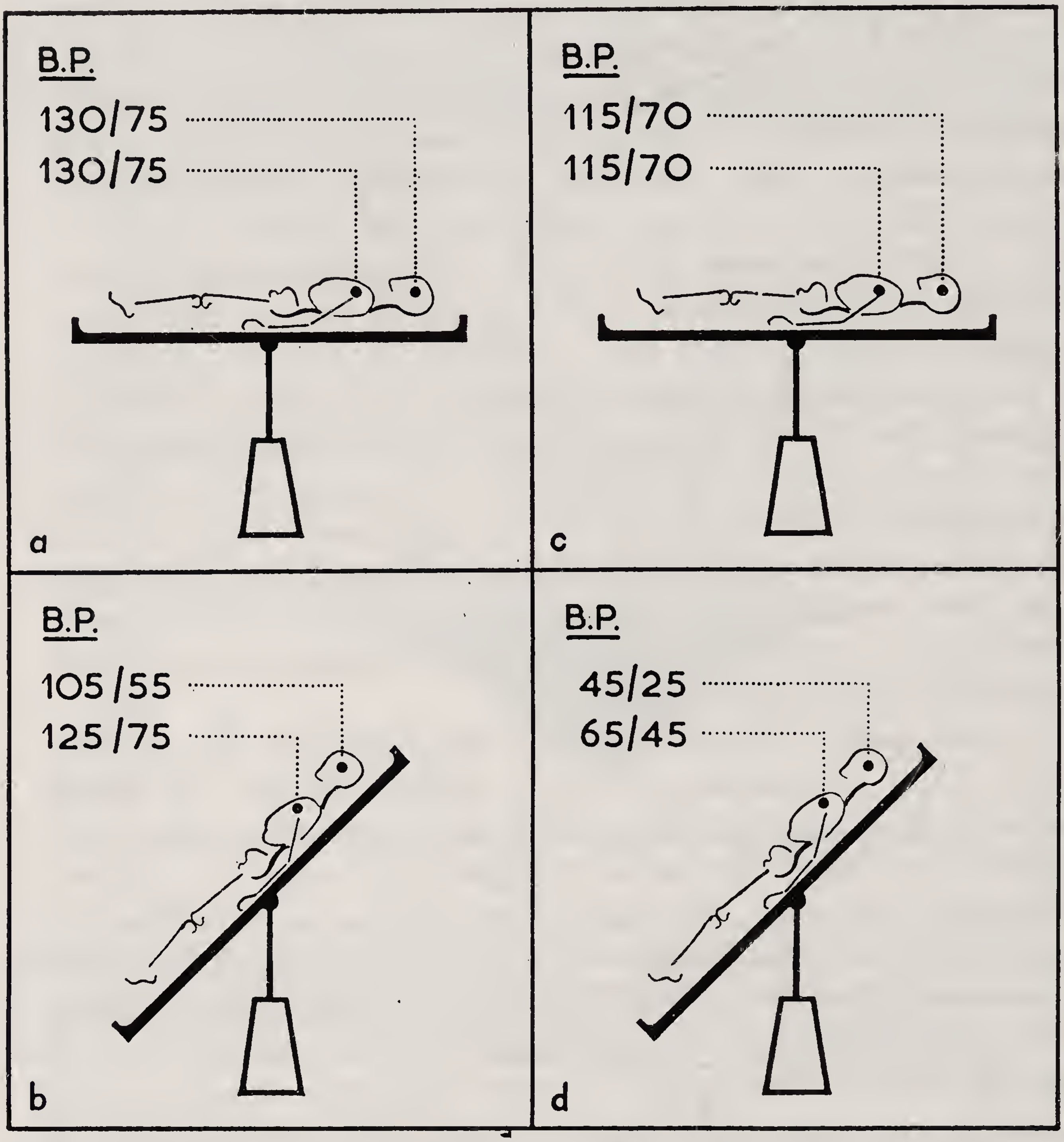

Fig. 7. Diagram of the effect of change of posture on the blood pressure before (a and c) and after (b and d) hexamethonium.

But in all these cases there are obvious stimuli at work (raised intrapulmonary pressure, haemorrhage, posture), and it is relatively easy to relate the action of the drug to the reflexes involved. It is a rather different matter to assess how far under normal undisturbed conditions there is a continuous autonomic tone. For instance, in an audience sitting listening to a speaker, how far are the viscera or the skin or the heart-rate being influenced by autonomic impulses of various kinds? We know the paths are there, but are they being used? One of the uses of hexamethonium may be, perhaps, that it will tell us a good deal about these paths. To illustrate the sort of information that it should be possible to obtain, I have compiled a list of actions which have already been described in patients receiving hexamethonium (Table 3). One can infer from these observations that there is for instance a steady neurogenic lubrication of the mucous surfaces (i.e. the conjunctiva, the nose and the mouth, and throat), and of the skin and scalp. They illustrate, too, how the normal vasoconstrictor tone of the skin must be an important sluice damming back heat within the body; and they bring to light a tone in the conjunctival vessels not commonly recognized.

The Hexamethonium Man. To summarize what I have said about the background autonomic tone, I would like to be frivolous for a moment and to bring together all the actions described, supposing them all exerted in one individual, an entirely hypothetical individual, whom we could call the 'hexamethonium man'. He is a pink-complexioned person, except when he has stood in a queue for some time, when he may get pale and faint. His handshake is warm and dry. He is a placid and relaxed companion; he may laugh, but he can't cry because the tears cannot come. Your rudest story will not make him blush and the most unpleasant circumstances will fail to make him turn pale. His wife will testify that his collars and socks stay very clean and sweet. He wears corsets and may, if you meet him out, be rather fidgety (the corsets compress his splanchnic vascular pool, the fidgets keep the venous return going from his legs). He dislikes speaking much unless helped with something to moisten his dry mouth and throat. He is rather long-sighted and easily blinded by bright light. The redness of his eye-balls may suggest irregular habits and in fact his head is rather weak. But he always behaves like a gentleman and never belches nor hiccups. He tends to get cold and keeps well wrapped up. But his health is good; he does not have chilblains and those diseases of modern civilization, hypertension and peptic ulcer pass him by. He is thin because his appetite is modest; he never feels hunger pains and his stomach never rumbles. He gets rather constipated so that his intake of liquid paraffin is high. As old age comes on frequency, precipitancy and strangury will not worry him, but he will suffer from retention of urine and impotence. One is uncertain how he will end, but perhaps, if he is not careful, by eating less and less and getting colder and colder, he will sink into a symptomless, hypoglycaemic coma and (like the universe) die a sort of entropy death.

TABLE 3. Effects of Hexamethonium in Man: I

SIGN OR SYMPTOM	AUTONOMIC PATHWAY BLOCKED
	Sympathetic supply (adrenergic)
Injection of conjunctivae	to conjunctival vessels
Flushing of skin and capillary pulsation	to arterioles of skin
Rise in skin temperature	,, ,,
Rise in skin blood flow	,, ,,
Rise in limb blood flow (leg arm)	to skin and muscle vessels and veins (?)
Reduction of cold pressor response	to arterioles and veins (?) of skin, muscle and viscera
Postural hypotension: sensitivity to lifts	,, ,,
Reduction of bleeding at operation	,, ,,
Dilatation of retinal vessels	to retinal vessels
Fall in body temperature	to arterioles of skin
Relief of causalgia	to arterioles of affected region
Sensitization to insulin	to adrenal medulla
	Sympathetic supply (cholinergic)
Dry scalp and dry skin	to sweat glands
Reduction of reflex sweating	,, ,,

This is a caricature, but it was worth perpetrating to emphasize the point that it is crucial to know what our background autonomic tone is; and that it is already possible to glean a good bit of information about it from clinical reports already available.

4. REACTIONS TO GANGLIONIC BLOCK

A final element in the complexity of the response to ganglionic block must be considered. If one functionally removes a large part of the autonomic nervous system, it is only to be expected that some sort of reaction, in an attempt to compensate for it, will take place. It was mentioned earlier that in patients treated for hypertension, a tolerance to hexamethonium steadily develops. It never seems to become absolute, and usually falls in blood pressure can still be obtained if a big enough dose is given. The tolerance passes away again if the treatment is stopped and can be re-established if treatment is resumed. The question arises whether this is due to a generalized ganglionic tolerance or whether it is something specific to the blood pressure. There is definite evidence that so far as certain parasympathetic ganglia are concerned, this tolerance either does not develop or develops much more slowly (Morrison, 1953). In a group of patients in whom the dose of hexamethonium has had to be steadily increased in order to produce a roughly constant effect on the blood pressure, the incidence of paralysis of accommodation, of the bladder, and of the intestine steadily rises. It is possible that there is a slight accommodation of this sort affecting all ganglia, but it is certain that such accommodation is not the whole story. It is necessary to look elsewhere for an explanation, and so far none is yet available.

Table 3. Effects of Hexamethonium in Man: II

Sign or Symptom	Autonomic Pathway Blocked
	Parasympathetic supply (*cholinergic*)
Paralysis of ocular accommodation and reaction to light	Ciliary ganglion
Dryness of eyes	Sphenopalatine ganglion
Dryness of mouth and nose	Otic ganglion and chorda tympani
Dryness of larynx	Vagal ganglia—in larynx
Tachycardia	Vagal ganglia—in heart
Diminished motility of stomach and small intestine	Enteric ganglia
Constipation	,, ,,
Ileus	,, ,,
Diminished secretion of gastric juice:	
spontaneous	,, ,,
nocturnal	,, ,,
in response to insulin	,, ,,
Depression of bladder reflexes	Pelvic nerve ganglia
Impotence	,, ,, ,,

A more usual reaction to a fall in blood pressure is, of course, an increased activity of certain autonomic pathways. It is worth

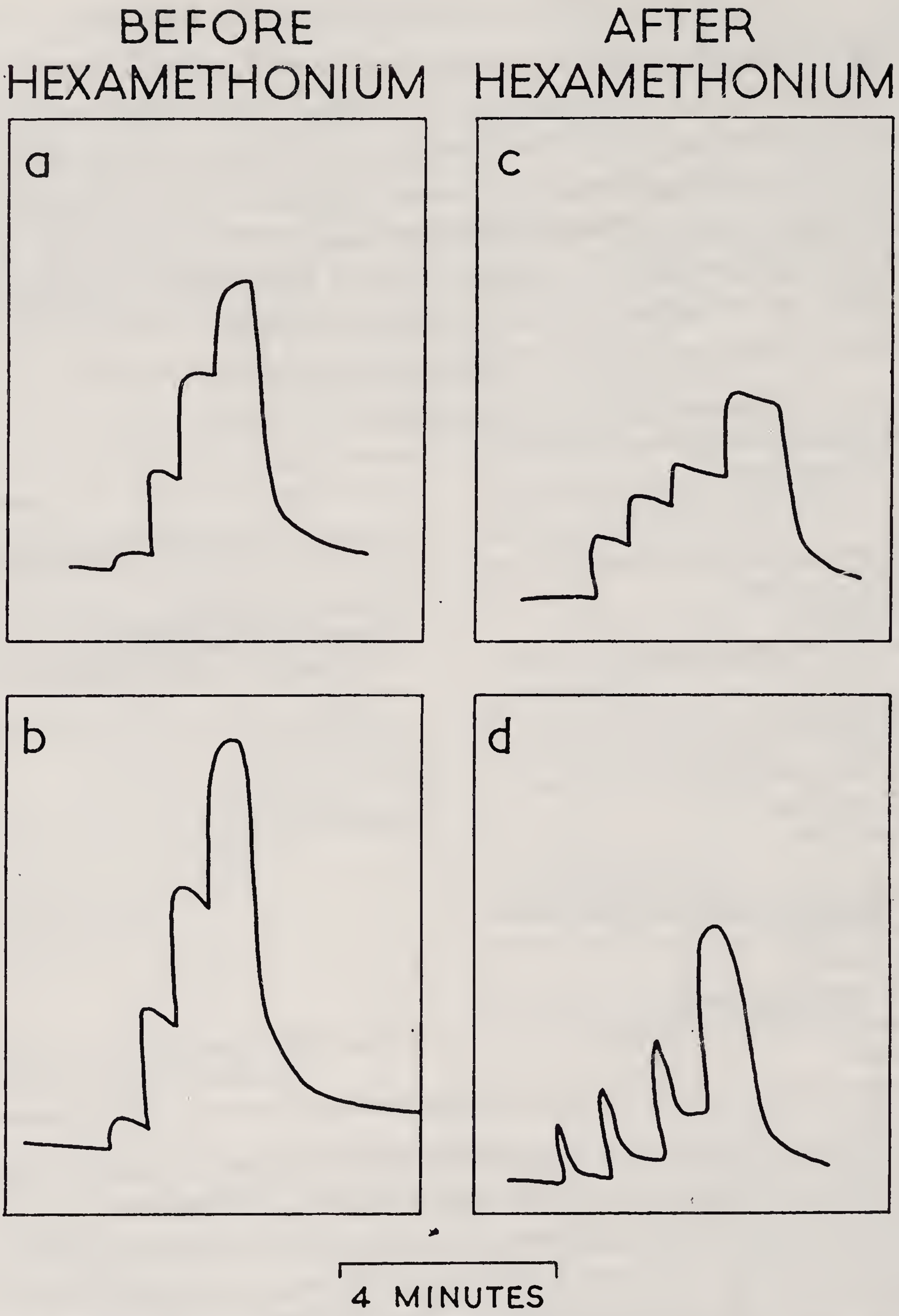

Fig. 8. Records of contraction of the cat's nictitating membrane excited by stimulation of the preganglionic cervical sympathetic trunk at 10 (a and c) and at 20 (b and d) shocks per second before and after hexamethonium. In each record, the stimulus strength was increased from zero to maximal in four successive steps each lasting one minute.

Despite the partial block by hexamethonium, the recruitment of more preganglionic nerve fibres (and hence of more ganglion cells) enables the total postganglionic discharge to be increased.

making a distinction here between what can be referred to briefly but loosely as 'recruitment' and 'acceleration'. One could envisage an intensification of autonomic activity in two ways, either the recruitment into action of fibres previously inactive, or the acceleration of the rate of discharge down fibres already excited. The two responses can be roughly imitated with the cat's nictitating membrane excited through the cervical sympathetic with the superior cervical ganglion as a relay station between the two. In Fig. 8 is reproduced a rather crude recruitment obtained by increasing the stimulus strength to the nerve fibre in four steps. In the normal preparation this brings successive increases in activity of the nictitating membrane. On the other side of the figure the same thing has been done after hexamethonium. As one would expect, although the ganglia rapidly fatigues, nevertheless the recruitment of successive fibres does actually confer some benefit. So that it may be said that in the presence of ganglionic block by hexamethonium a successful reaction could take place by recruitment, provided that the block was not so intense as to paralyse completely these newly activated synapses as well, or so intense that they fatigued rapidly to insignificant levels, when the reaction would only be a transient one.

But the second kind of response, by *acceleration*, is rather a different story. In Fig. 9 are the results of two experiments on a ganglion that is partially paralysed. At the top are the contractions which the ganglia will normally produce to excitations of one, ten and twenty shocks a second. When the ganglion is partially paralysed, an acceleration of rate of discharge from one a second to ten a second does in fact produce some increase in the contraction height. But the acceleration from ten a second to twenty a second actually weakens the final contraction. We have therefore a situation in which the benefit obtained by increasing the rate of autonomic discharge is rather severely limited. Of course there is a similar 'ceiling' in normal ganglia where you can produce fatigue by stimulating at very high frequencies. The characteristic effect of hexamethonium is not the establishing of a ceiling but of bringing it down to comparatively low levels of stimulation rate.

One important application of this may be when the reaction involves the release of adrenaline. Under normal conditions the autonomic activation of the adrenals appears to be negligible. It follows that, when activity is initiated, the preganglionic discharge rate is likely to be quite low, still well below its 'ceiling', and thus resistant to hexamethonium. Thus the apparently paradoxical situation could readily arise in which a vigorous adrenal discharge could take place in the presence of ganglionic block by hexamethonium sufficiently intense to lower the blood pressure enough to excite the adrenal response. Dr. Morrison and Dr. Enderby tell me that they have quite often observed responses to hexamethonium which they were strongly tempted to believe were of this kind. One may compare this with what might be expected from the general vasoconstrictor fibres in a case of hypertension. One must assume that in this patient, supposing him to be of the neurogenic type, there is a considerable activity in the vasoconstrictor fibres already. If in such a patient the blood pressure is lowered by hexamethonium, reaction to this by increasing the rate of autonomic discharge will have little effect, or may even lead to a more intense paralysis (as in Fig. 9).

These are rather theoretical considerations. But with care it might be possible to use them to illuminate clinical practice. In general, one might expect that those reactions to the effects of ganglionic block which are fresh and are not normally active will be more successful than reactions involving intensification of activities habitually in play.

Conclusion

The general trend of the argument has been to multiply reasons for the variation of the actions of hexamethonium in man; reasons such as differences in sensitivity of various ganglia, in absorption, distribution and excretion of the drug, in the existence of autonomic tone and in its intensity, and in the reactions to ganglionic block which may take place. It makes a formidable list and lends weight to the occasional clinical complaint that such drugs are unreliable in action. Yet, under standard condition in anaesthetized animals, they are extremely consistent in

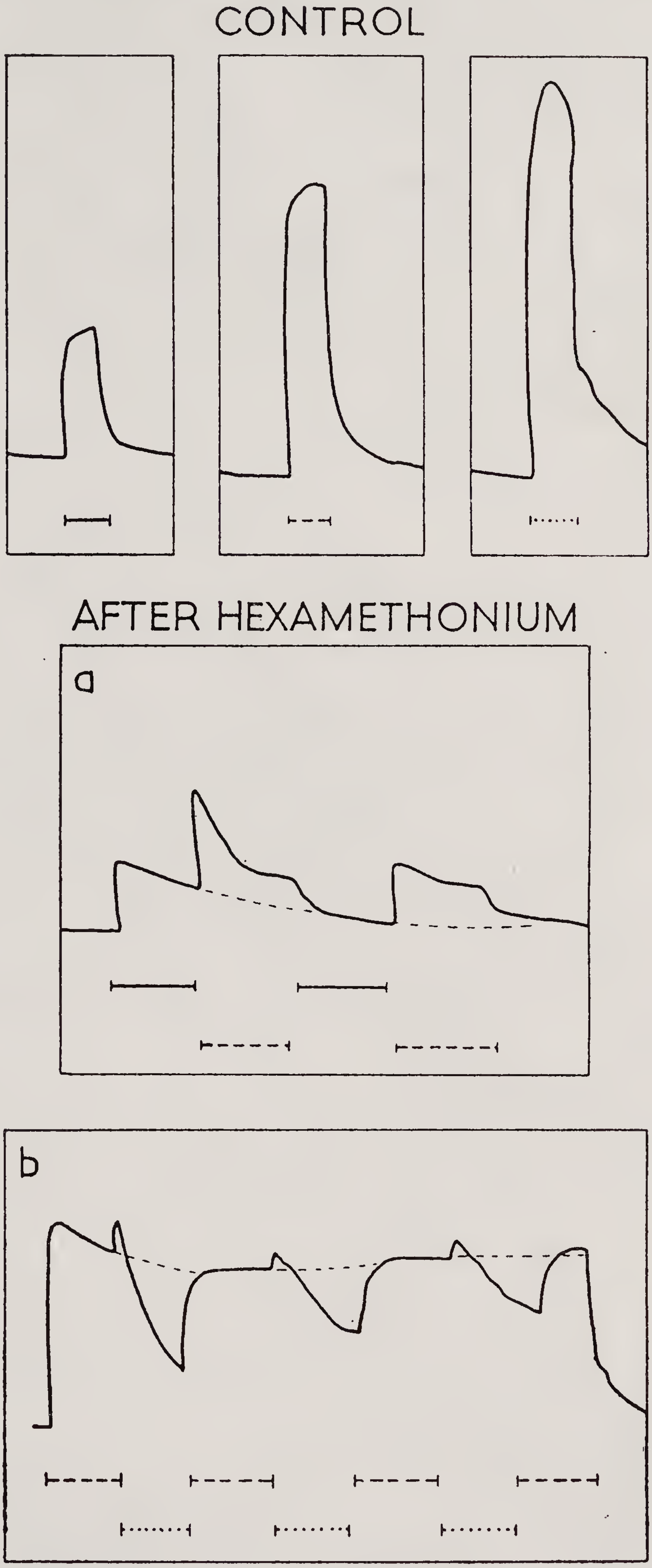

Fig. 9. Records of contraction of the cat's nictitating membrane excited by stimulation of the preganglionic cervical sympathetic trunk at 1, 10 or 20 shocks per second (denoted by continuous, broken and dotted lines respectively). Above are the responses to these rates of stimulation, for one minute, in a normal cat. Below are the responses obtained after hexamethonium.

Increasing the rate of stimulation in the presence of hexamethonium does not necessarily lead to a bigger postganglionic response; although the change from 1/second to 10/second in (a) does so, the further acceleration from 10/second to 20/second in (b) actually produces (after an initial augmentation) a considerable increase in block.

their behaviour. But if one considers the situation in man, it is perhaps not very surprising that such variation exists. The autonomic nervous system pervades the whole body; it carries all the play of emotions and nervous influences into their visceral expression; and everyone differs in these as much as in their physical structure. The issue might therefore be put in a different way; that there is, in our present wealth of somewhat uncontrollable responses and of unanswered questions, a really rich field for greatly increasing our knowledge of normal and pathological autonomic function.

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